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<p>(21) International Application Number: PCT/EP92/00717</p> <p>(22) International Filing Date: 28 March 1992 (28.03.92)</p> <p>(30) Priority data:</p> <table> <tr> <td>9106686.0</td> <td>28 March 1991 (28.03.91)</td> <td>GB</td> </tr> <tr> <td>9114678.7</td> <td>8 July 1991 (08.07.91)</td> <td>GB</td> </tr> <tr> <td>9200389.6</td> <td>9 January 1992 (09.01.92)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for GB only): HOLMES, Michael, John [GB/GB]; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).</p> <p>(71) Applicant (for all designated States except US): NYCOMED AS [NO/NO]; Nycoveien 2, P.O. Box 4220 Torshov, N-0401 Oslo 4 (NO).</p>		9106686.0	28 March 1991 (28.03.91)	GB	9114678.7	8 July 1991 (08.07.91)	GB	9200389.6	9 January 1992 (09.01.92)	GB	<p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): KLAIVENESS, Jo [NO/NO]; Skøyen terasse 15, N-0276 Oslo (NO). RONGVED, Pål [NO/NO]; Hovdens vei 13, N-1454 Helvik (NO). STRANDE, Per [NO/NO]; Nordengveien 78A, N-0755 Oslo (NO).</p> <p>(74) Common Representatives: HOLMES, Michael, John et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), NO, SE (European patent), US.</p> <p>Published With international search report.</p>	
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<p>(54) Title: CROSS-LINKING AGENT</p> <p>(57) Abstract</p> <p>Cross-linking agents containing or adapted to generate methylene diester or diamide groups of formula -(Z)_m-Y-X-C(R¹R²)_n-X-Y-(Z)_n- (where each X and Z is selected from -O-, -S- and -NR- (where R is hydrogen or an organic group); each Y is carbonyl, thiocarbonyl, sulphonyl, phosphoryl or a similar acid-forming group; m and n are each zero or 1; and R¹ and R² are each hydrogen, an organic group or a group -X-Y(Z)_m-, or together form a divalent organic group) are useful in the preparation of substrates containing biodegradable cross-linking groups.</p>												

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CROSS-LINKING AGENT

5 This invention relates to novel crosslinking agents, more particularly to crosslinking agents capable of generating biodegradable crosslinking groups.

The use of crosslinking agents in fields such as protein and polymer chemistry is widespread and well known, e.g. for investigative or stability-enhancing purposes. The possibility of deliberately introducing biodegradable crosslinking groups has not hitherto been disclosed, but has been found by us to possess a substantial number of utilities, for example in the preparation of biodegradable polymers (e.g. as described in our copending International Patent Application No. PCT/EP91/01751), in the attachment of drugs or agricultural chemicals to polymer systems (e.g. to provide delayed release delivery systems), and in the preparation of stabilised but biodegradable and therefore rapidly eliminable ultrasound contrast agents based on microbubbles encapsulated by crosslinked liposomes or crosslinked proteins (e.g. as described in our copending British Patent Applications Nos. 9106673.8 and 9106686.0 respectively) or on microparticles of crosslinked carbohydrates, X-ray contrast agents, polypeptides and proteins (e.g. as described in our copending British Patent Application No. 9114570.6); the contents of the specifications of the aforementioned applications are herein incorporated by reference.

The crosslinking agents of the invention are characterised in that they contain, or are capable of generating during crosslinking, methylene diester or diamide groups in which the ester or amide residues are derived from a range of carbon, sulphur and phosphorus acids. Such groups are particularly rapidly degraded by common esterase enzymes but are stable in the absence of

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enzymes.

A small number of compounds falling within this definition have previously been described in the literature and these specific compounds per se are excluded from the scope of the invention. Thus, for example, US-A-2341334 describes methylene dimethacrylate, ethylidene dimethacrylate and butylidene dimethacrylate as being copolymerisable with ethylenically unsaturated monomers such as vinyl acetate, methyl methacrylate or styrene; DD-A-95108 describes the preparation of benzylidene dimethacrylate and 2,2,2-trichloroethylidene dimethacrylate; US-A-2839572 describes the preparation of a number of alkenylidene crotonates such as allylidene dicrotonate, methallylidene dicrotonate and 2-chloroallylidene dicrotonate; US-A-2568501 describes the preparation of heptafluorobutylidene diacrylate; propylidyne trimethacrylate is described by Kimura H. in J. Osaka Univ. Dent. Sch., 20 (1980), pp. 43-49; propylidyne triacrylate is described by Cox R.J. in Polym. Prep. (Am. Chem. Soc., Div. Polym. Chem.) 29 (1988), pp. 122-123; and allylidene diacrylate and allylidene dimethacrylate are described by Arbuzova A. et al. in Zh. Obshch. Khim. 26 (1956), pp. 1275-1277. Other disclosures of the use of certain of these compounds as monomers, comonomers or crosslinking agents include Szymczak T.J. et al. in Modern Plastics (August 1974), pp. 66-68 and in West. Elec. Eng. 18 (1974), pp. 26-30; DE-A-1104700; and FR-A-2119697. Crosslinking involving the use of N,N'-methylenebis(acrylamide), and in certain cases N,N'-methylenebis(methacrylamide), is described in, for example, US-A-4 743 267, US-A-4 962 170, US-A-5011864, EP-A-0383124, EP-A-0383126, CA-A-1249952, and by Capek et al., Makromol. Chem. 191 (1990), pp. 121-138 and 192 (1991), pp. 2031-2040, and Latha et al., J. Appl. Polym. Sci. 43 (1991), pp. 1159-1163.

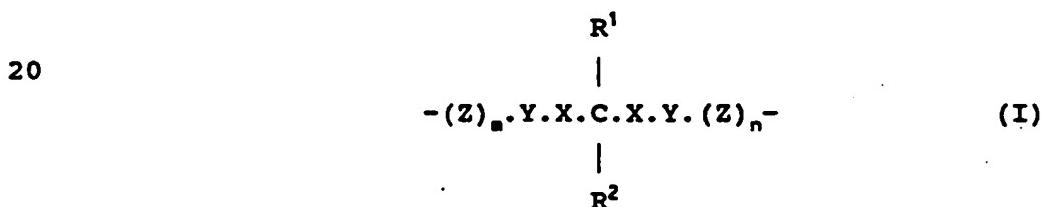
There is no suggestion in any of the above prior

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art that the methylene di(carboxylic ester) or N,N'-di(carboxamide) groupings resulting from polymerisation or crosslinking might be biodegradable; indeed, the introduction of crosslinking groups of this type is generally seen as conveying enhanced rigidity and/or stability. The present invention accordingly embraces the use of these known compounds in the preparation of biodegradable crosslinked structures.

It should be noted that in the prior art crosslinking methylene di(carboxylic ester) groups are invariably present as simple carbon-attached ester groups, as a consequence of their introduction by free radical propagated reactions of e.g. alkylidene diacrylates or dimethacrylates.

Subject to the foregoing disclaimer, the novel compounds of the present invention may be regarded as crosslinking agents containing a group of formula



[in which each X, which may be the same or different, is selected from -O-, -S- and -NR-, where R represents a hydrogen atom or an organic group; each Y, which may be the same or different, represents carbonyl, thiocarbonyl, sulphonyl or phosphoryl (i.e. a group of formula



where R³ is a hydrogen atom or an organic group) or a

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similar acid-forming group; each Z, which may be the same or different, is selected from -O-, -S- and -NR-, where R represents a hydrogen atom or an organic group; m and n, which may be the same or different, are each 5 zero or 1; and R¹ and R², which may be the same or different, are each selected from hydrogen atoms, monovalent organic groups and groups of formula -X.Y.(Z), - as hereinbefore defined, or R¹ and R² together form a divalent organic group] or containing a group 10 adapted to generate a group of formula (I) upon reaction with a reagent or substrate containing a species H.X.Y.(Z), - or a reactive derivative thereof.

The term "crosslinking" as used herein denotes the introduction of any desired proportion of crosslinking 15 groups and thus generally embraces the preparation of copolymers containing linkages of formula (I).

Organic groups represented by R, R¹, R² and R³ may, for example, each be a hydrocarbyl or heterocyclic group, for example having 1-20 carbon atoms, e.g. an 20 aliphatic group such as an alkyl or alkenyl group (preferably having up to 10 carbon atoms), a cycloalkyl group (preferably having up to 10 carbon atoms), an araliphatic group such as an aralkyl group (preferably having up to 20 carbon atoms), an aryl group (preferably 25 having up to 20 carbon atoms) or a heterocyclic group having up to 20 carbon atoms and one or more heteroatoms selected from O, S and N; such a hydrocarbyl or heterocyclic grouping may carry one or more substituents such as halogen atoms or groups of the formulae -NR⁴R⁵, -CONR⁴R⁵, -OR⁶, -SR⁶ and -COOR⁷ (where R⁴ and R⁵, which may be the same or different, are hydrogen atoms, acyl groups 30 or hydrocarbyl groups as defined for R, R¹, R² and R³; R⁶ is a hydrogen atom or an acyl group or a group as defined for R, R¹, R² and R³; and R⁷ is a hydrogen atom or 35 a group as defined for R, R¹, R² and R³). Where R¹ and R² represent a divalent grouping, this may be an alkylene, alkenylene, alkylidene or alkenylidene group (preferably

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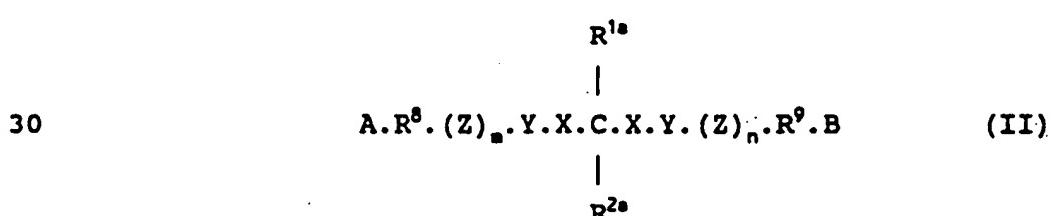
having up to 10 carbon atoms) which may carry one or more substituents as defined above. In general R, R¹, R² and R³ are preferably H or small groups such as C₁₋₄ alkyl groups.

5 Aliphatic groups R, R¹, R² and R³ may be straight or branched, saturated or unsaturated, and include, for example, alkyl and alkenyl groups such as methyl, ethyl, isopropyl, butyl and allyl. Araliphatic groups include (monocarbocyclic aryl) alkyl groups such as benzyl.

10 Aryl groups include mono- and bi-cyclic groups such as phenyl, tolyl and naphthyl. Heterocyclic groups include 5- and 6-membered rings preferably containing a single heteroatom, such as furyl, thienyl and pyridyl.

Possible substituents in hydrocarbyl groups R, R¹, R² and R³ include hydroxyl, etherified hydroxyl (e.g. C₁₋₅ alkoxy such as methoxy), esterified hydroxyl (e.g. C₁₋₆ acyloxy such as acetoxy), etherified thiol, N-(C₁₋₆ alkyl)amino, N-(C₁₋₆ acyl)amino, N-(C₁₋₆ acyl)-N-(C₁₋₆ alkyl)amino, carbamoyl, N-(C₁₋₆ alkyl) carbamoyl and halogen. Aromatic rings may carry C₁₋₆ alkyl groups, e.g. as in tolyl groups. Substituents may be present in combination and thus, for example, N-acyl and N-alkyl groups may carry hydroxyl or etherified or esterified hydroxyl groups:

25 One preferred class of compounds according to the invention may be represented by the formula



(wherein X, Y, Z, m and n are as hereinbefore defined; R^{1a} and R^{2a} are as defined for R¹ and R² except that they may represent groups -X.Y.(Z)_m.R⁸.A or -X.Y.(Z)_n.R⁹.B rather than groups -X.Y.(Z)_m; R⁸ and R⁹, which may be the same

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or different, represent divalent organic groups optionally interrupted by one or more heteroatoms and/or carrying one or more substituents containing heteroatoms; and A and B, which may be the same or 5 different, optionally in conjunction with the groups R⁸ and R⁹ to which they are attached, represent functional groupings reactive with the species to be crosslinked; with the proviso that when both A.R⁸- and -R⁹.B represent optionally substituted lower alk-1-enyl groups, both of 10 X represent -O- or -NR- and both of Y represent

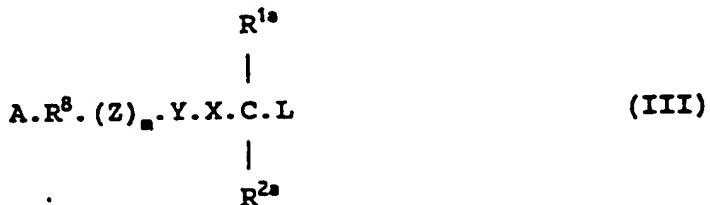


15

then at least one of m and n is 1).

A second preferred class of compounds according to the invention may be represented by the formula

20



25

(wherein X, Y, Z, m, R^{1a}, R^{2a}, R⁸ and A have the above-defined meanings and L is a leaving group). Such compounds may be reacted with compounds of the formula

30



(where X, Y, Z and n are as hereinbefore defined and R¹⁰ represents a hydrogen atom or an organic group), or appropriate reactive derivatives thereof (e.g. alkali 35 metal salts of compounds of formula (IV) which are acids), to generate a biodegradable linkage of formula (I).

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It will be appreciated that R^{10} may represent an organic group such that, for example, the compound (III) reacts to form a compound of formula (II) or a precursor therefor. Alternatively the group R^{10} may represent a 5 substrate which is to be crosslinked; in addition to the $-(Z)_n.Y.X.H$ substituent or reactive derivative thereof such a substrate will also possess a functional grouping reactive with $-A$ or $-R^8A$ in formula (III).

The divalent organic groups R^8 and R^9 in the above 10 formulae may, for example, be selected from alkylene and alkenylene groups (e.g. containing up to 30, more preferably up to 20, e.g. 1-10, carbon atoms), cycloalkylene groups (preferably having up to 10 carbon atoms), arylene groups (containing one or more aromatic 15 rings and preferably having up to 20 carbon atoms), aralkylene groups (preferably having up to 20 carbon atoms and which may be bonded via the aryl and/or alkyl moieties - such aralkylene groups include, for example, two aryl groups joined by an alkylene chain), and 20 heterocyclic groups (having one or more heteroatoms preferably selected from O, N and S and preferably having up to 20 carbon atoms). The groups may carry substituents, e.g. as set out above for R , R^1 , R^2 and R^3 and/or substituents such as oxo or thio groups. The 25 carbon chains may be interrupted by heteroatoms such as O, N, S or P, e.g. in conjunction with oxo substituents, to form linkages such as ether, ester, thioester or amide groups. The presence of disulphide linkages may also be advantageous by virtue of their inherent 30 biodegradability.

It will be appreciated that groups R^8 and/or R^9 may be chosen so as to include one or more further groups of formula (I) and that the grouping $-R^8.A$ in formula (III) may be such that it terminates in a grouping R^{1a} .

35

$-(Z)_n.Y.X.C.L$

R^{2a}

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(where X, Y, Z, m, R^{1a}, R^{2a} and L are as hereinbefore defined) capable of generating a biodegradable linkage of formula (I).

The nature of functional groups A and B will clearly depend on the nature of the species which is to be crosslinked or otherwise reacted, in particular the nature of reactive functional groupings present therein. It will be appreciated that numerous complementary pairs of interacting functional groups are known in the art, e.g. as described by Beaumert *et al.* in "Crosslinking techniques" (Meth. Enzymol. 172 (1989), pp. 584-609) or in the Pierce Handbook and General Catalogue (1989), pp. 284-311.

Thus, for example, hydroxyl groups in substrates such as carbohydrates may be reacted as described in "Advances in Carbohydrate Chemistry and Biochemistry" ed. by R. Stuart Tipson and D. Horton, 33 (1976), pp. 11-109. Examples of appropriate functional groups for reacting with such substrates include halogen atoms such as chlorine or bromine, e.g. in the form of acyl halides such as alkanoyl or sulphonyl halides; sulphonyloxy groups, e.g. alkanesulphonyloxy groups such as mesyloxy groups and arenesulphonyloxy groups such as tosyloxy groups; α -halomethyl ester and keto groups; activated carboxyl groups such as symmetrical or mixed anhydrides; activated hydroxyl groups; activated alkenes, e.g. α,β -unsaturated esters, amides and ketones; conjugated diyne and enyne systems; epoxy groups; and acetal-forming aldehyde and ketone groups and derivatives thereof such as enol ethers or acetal or ketal groups.

Amino groups in substrates such as proteins may, for example, be reacted with functional groups such as activated carboxyl groups (e.g. N-hydroxysuccinimidyl derivatives, especially water solubility-enhanced sulphonated N-hydroxysuccinimidyl derivatives), imidoesters, nitroaryl halides, nitrene precursors (e.g. aryl azides such as phenylazido), carbene precursors

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(e.g. diazo compounds and diazirines), aldehydes, ketones, isocyanates, isothiocyanates, semicarbazides and thiosemicarbazides, epoxides, phenol esters (e.g. nitrophenol esters), acyl azides and hydrazines, haloformates, and acyl halides (e.g. alkanoyl chlorides or sulphonyl chlorides such as mesyl or tosyl chloride).

Carboxyl groups may, for example, be reacted with functional groups such as hydroxyl, mercapto, amino or diazo.

10 Sulfhydryl groups may, for example, be reacted with functional groups such as maleimides, sulphonated maleimides, α -halomethyl carbonyl derivatives (e.g. esters, amides or ketones), alkyl or aralkyl halides, nitrosoureas, s-triazines, aziridines and pyridyl disulphides.

15 Substrates containing ethylenically or acetylenically unsaturated carbon-carbon bonds (e.g. vinyl monomers such as vinyl acetate or styrene, or acrylic or methacrylic monomers such as acrylic acid, 20 methacrylic acid, methyl acrylate, methyl methacrylate, acrylamide, methacrylamide, acrylonitrile, methacrylonitrile, hydroxyethyl methacrylate or hydroxypropyl methacrylate) may be copolymerised with compounds of formula (II) in which A and B comprise e.g. 25 ethylenically unsaturated groups, for example under conditions appropriate for free radical polymerisation, to yield polymers containing biodegradable crosslinking groups of formula (I). It will be appreciated that in such circumstances the groups A and B may if desired 30 form unsaturated groups in conjunction with R⁸ and R⁹ respectively; thus, for example, A.R⁸- and/or -R⁹.B may each represent optionally substituted vinyl groups.

Leaving groups L in compounds of formula (III) include halogen atoms such as chlorine or bromine and 35 sulphonyloxy groups such as mesyloxy or tosyloxy.

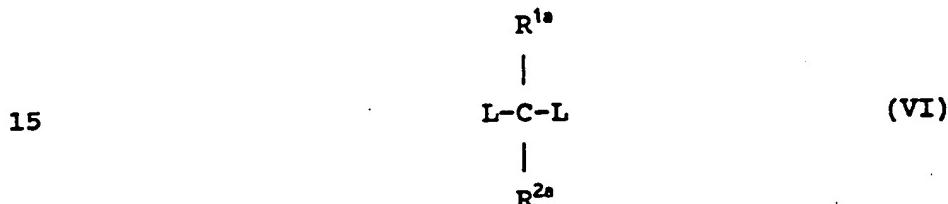
Compounds in accordance with the present invention may be prepared by any convenient method. Thus, for

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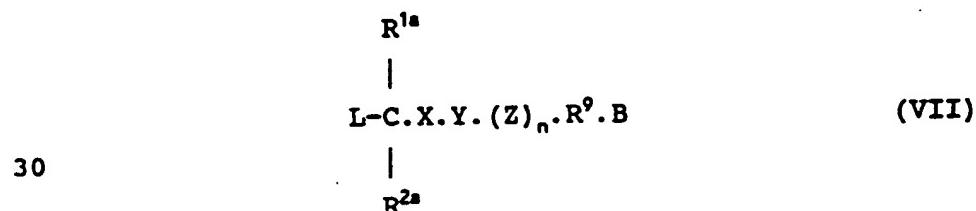
example, one or two equivalents of a compound of formula



5 (where X, Y, Z, m, R⁸ and A are as hereinbefore defined, subject, if necessary and/or desired to A and any other reactive groups being protected), or a functional derivative thereof (e.g. a salt, for example an alkali metal salt such as the potassium or cesium salt of a
10 compound (V) which is an acid), may be reacted with one equivalent of a compound of formula



20 (where R^{1a}, R^{2a} and L are as hereinbefore defined) to yield compounds of formula (III) and symmetrical compounds of formula (II) respectively. Alternatively, if an unsymmetrical compound of formula (II) is required, one may, for example, react equivalent quantities of a compound of formula (V), or a functional derivative thereof, and a compound of formula



30 (where X, Y, Z, n, R^{1a}, R^{2a}, R⁹, B and L are as hereinbefore defined, subject if necessary and/or desired to B and any other reactive groups being protected). Such reactions will normally be carried out in solution, for example in a polar solvent such as

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dimethylformamide.

Symmetrical compounds of formula (II) in which R^{2a} represents a hydrogen atom, m and n are zero, each Y represents a carbonyl group and each X represents -O- may also be prepared by reacting a compound of formula

5



(where A and R⁸ are as hereinbefore defined, subject, if necessary and/or desired to A and any other reactive groups being protected) with an aldehyde of formula

10



15 (where R^{1a} is as hereinbefore defined) in the presence of an acid catalyst such as hydrochloric acid; if desired water may be removed from the reaction mixture by azeotropic distillation.

20 Compounds of formula (III) in which L is a halogen atom may also be prepared by reaction of a compound of formula (V) as hereinbefore defined, particularly such a compound in which Y represents a carbonyl group and X represents -O-, with an aryl thioether of formula

25



|



(X)

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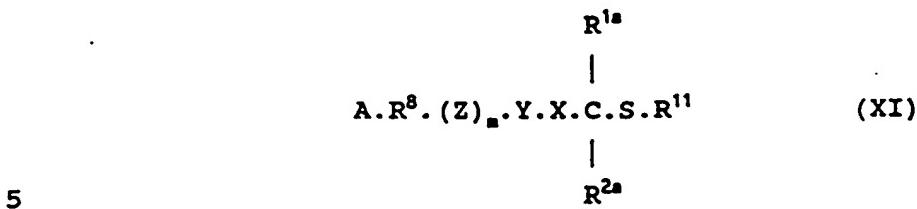
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(where R^{1a} and R^{2a} are as hereinbefore defined and R¹¹ represents an aryl group such as phenyl), e.g. in a polar solvent such as dimethylformamide in the presence of a base such as pyridine, to yield a compound of

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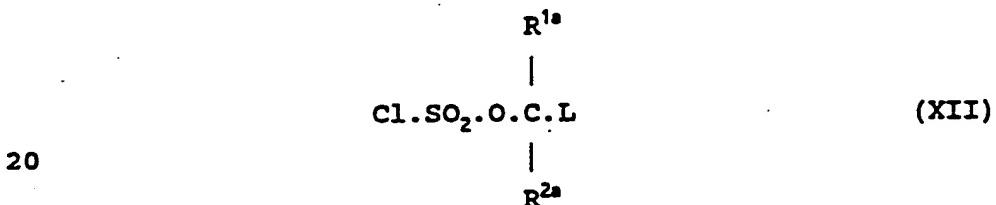
formula

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(wherein all the symbols are as hereinbefore defined) and halogenating this thioether, e.g. by reaction with sulfuryl chloride in a solvent such as dichloromethane or with bromine in a solvent such as carbon tetrachloride, to yield a compound (III) in which L is chlorine or bromine respectively.

Alternatively, compounds of formula (III) may be prepared by reaction of a compound of formula (V), as hereinbefore defined, with a chlorosulphate of formula



(wherein R^{1a}, R^{2a}, and L are as hereinbefore defined, L preferably being chlorine), e.g. using the method of Binderup *et al.* described in *Synth. Comm.* 14(9) (1984), pp. 857-864.

Protecting groups used in connection with A and B and any other reactive groups present may, for example, be those conventional in the art. Thus, for example, carboxyl groups may be protected using reductively cleavable ester groups such as benzyl, and hydroxyl groups may be protected using acid cleavable etherifying groups such as triphenylmethyl.

One may also prepare compounds of formulae (II) and (III) containing precursors for the desired A.R⁸- (and/or -R⁹.B groups where appropriate) and subsequently convert such precursor groups to the desired reactive groupings.

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Thus, for example, compounds in which A and/or B represent epoxide groups may be prepared by oxidation of precursors containing appropriately positioned (e.g. terminal) ethylenically unsaturated bonds (e.g. using an

5 oxidising agent such as metachloroperbenzoic acid), or by reacting compounds containing appropriately positioned hydroxyl groups (e.g. phenolic hydroxyl groups) with reagents such as epichlorohydrin; compounds in which A.R⁸- and/or -R⁹.B represent enol ether groups

10 may be prepared by, for example, acid-catalysed elimination from corresponding acetals or ketals.

Hydroxyl group-containing precursors may also be activated by, for example, reaction with sulphonyl halides such as mesyl or tosyl chloride to generate

15 reactive leaving groups such as mesylate or tosylate or with α,β -unsaturated alkenoyl halides such as acryloyl chloride to generate α,β -unsaturated esters.

Compounds of formula (VII) in which L represents a halogen atom may, for example, be prepared by reacting

20 compounds of formulae



and $\text{Hal.Y.(Z)}_n.R^9.B$ (XIV)

30 (where Hal represents a halogen atom and the remaining symbols have the above-defined meanings), e.g. in the presence of a base such as pyridine.

As hereinbefore indicated, the invention embraces the use of all compounds containing a group of formula

35 (I) or capable of reacting to generate such a group, including compounds of formula (II) subject to the foregoing proviso regarding the definitions of X, Y, m,

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n, R⁸, R⁹, A and B, in the preparation of substrates containing biodegradable crosslinking groups. Such uses include, for example, the previously mentioned covalent stabilisation of a range of ultrasound contrast agents, 5 thereby enhancing the duration of attenuative activity of such agents in vivo while permitting their ready subsequent elimination from the body, and the preparation of polymers useful in the manufacture of, for example, surgical implants, soft tissue prostheses, 10 sponges, films, wound dressings, flexible sheets, containers, plasticisers, delayed release formulations for drugs (e.g. steroids, contraceptives, antibacterials, narcotic antagonists and anti-tumour drugs) and agricultural chemicals (e.g. weed killers), 15 and polymer particles incorporating diagnostic agents (e.g. X-ray contrast agents).

Where previously disclosed reagents such as methylene diacrylate or dimethacrylate are used in accordance with this aspect of the invention, the 20 reaction conditions will be chosen so as to ensure biodegradability of the product, e.g. by using a non-free radical mechanism such as Michael addition of nucleophiles, for example with reactive substrate groups such as hydroxyl groups, or by effecting 25 copolymerisation with substrates such as acrylonitrile which may polymerise by non-radical mechanisms. Free radical polymerisations should desirably be effected in such a way as to avoid formation of excessively long or tightly crosslinked carbon chains, e.g. so as to produce 30 polymers having a molecular weight not exceeding 40,000.

The following non-limitative Examples serve to illustrate the invention.

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EXAMPLE 1

Methylene dimethacrylate

A solution of potassium hydroxide (1.00 M, 40.00 ml) is
5 added to methacrylic acid (3.44 g, 40.00 mmol) at 0°C and the solution freeze dried for 16 hours. Dry dimethylformamide (230 ml) is added and the suspension heated to 60°C under a dry nitrogen atmosphere.
10 Diiodomethane (1.61 ml, 20.00 mmol) is added in two portions during 10 min. and the reaction mixture left for 4 days at 60°C. The solvent is removed under reduced pressure (0.05 mm Hg), before diethyl ether (140 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml) are added. The aqueous layer is
15 extracted with diethyl ether (6 x 60 ml) and the combined ether extracts washed with water (4 x 50 ml), dried (MgSO_4), and evaporated to give 2.63 g (72%) of the title compound. ^1H NMR (60 MHz, CDCl_3): δ 1.97 (2 x CH_3 , m), 5.63 (2 x H-C=, m), 5.88 (CH_2 , s), 6.18 (2 x H-C=, m). IR (film, cm^{-1}): 2987 (w), 2962 (w), 2930 (w), 1732 (str), 1638 (w), 1454 (w), 1315 (w), 1295 (w), 1158 (w), 1100 (str), 1012 (m), 989 (m). This product may be used in accordance with the invention, for example to crosslink acrylamide polymers.

25

EXAMPLE 2

Methylene diacrylate

30 A solution of potassium hydroxide (1.00 M, 40.00 ml) is added to acrylic acid (2.88 g, 40.00 mmol) at 0°C and the solution freeze dried for 16 hours. Dry dimethylformamide (200 ml) is added and the suspension heated to 60°C under a dry nitrogen atmosphere.
35 Diiodomethane (1.61 ml, 20.00 mmol) is added in two portions during 10 min. and the reaction mixture left for 4 days at 60°C. The solvent is removed under

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reduced pressure (0.05 mm Hg), before diethyl ether (140 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and water (50 ml) are added. The aqueous layer is extracted with diethyl ether (6 x 60 ml) and the

- 5 combined ether extracts washed with water (4 x 50 ml), dried ($MgSO_4$), and evaporated to give 1.06 g (34%) of the title compound. 1H NMR (60 MHz, $CDCl_3$): δ 5.81-6.61 (2 x $CH_2 = CH-$, m), 5.84 (CH_2 , s). This product may be used in accordance with the invention, for example to
- 10 crosslink acrylic acid and methyl acrylate polymers.

EXAMPLE 3

Chloromethyl (2-methacryloyloxy)ethyl carbonate

- 15 Pyridine (0.89 ml, 11.00 mmol) is added dropwise to a solution of chloromethyl chloroformate (0.89 ml, 11.00 mmol) and 2-hydroxyethyl methacrylate (1.22 ml, 10.00 mmol) in dichloromethane (12 ml) at 0°C under a dry nitrogen atmosphere. After 21 hours at 20°C the reaction mixture is washed with hydrochloric acid (1.00 M, 10 ml), saturated aqueous sodium hydrogen carbonate (10 ml) and water (10 ml). The organic phase is dried ($MgSO_4$) and the solvent evaporated under reduced pressure (10 mm Hg) to give 1.97g (88%) of the title compound. 1H NMR (60 MHz, $CDCl_3$): δ 1.88 (CH_3 , d, $J=2$ Hz), 4.35 (O- CH_2-CH_2-O , m), 5.47 (H-C=, m), 5.63 (CH_2-Cl , s), 6.00 (H-C=, m).
- 20
- 25

30

EXAMPLE 4

(2-Methacryloyloxy)ethyl methacryloyloxymethyl carbonate

- 35 A solution of potassium hydroxide (1.00 M, 5.00 ml) is added to methacrylic acid (0.43 g, 5.00 mmol) at 0°C and the solution freeze dried during 16 hours. Dry dimethylformamide (50 ml) is added and to the resulting

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suspension is added chloromethyl (2-methacryloyloxy)ethyl carbonate (1.11 g, 5.00 mmol).

18-Crown-6 (0.066 g, 0.25 mmol) is added as a catalyst and the reaction left under a dry nitrogen atmosphere.

- 5 After 24 hours at 20°C and 6 days at 4°C the solvent is removed under reduced pressure (0.05 mm Hg) and diethyl ether (30 ml) and water (20 ml) added. The aqueous layer is extracted with diethyl ether (3 x 20 ml) and the combined ether extracts washed with water (20 ml),
10 dried ($MgSO_4$) and evaporated to give 1.26 g (93%) of the title compound. 1H NMR (60 MHz, $CDCl_3$): δ 1.97 (2 x CH_3 , m), 4.38 (O- CH_2 - CH_2 -O, m), 5.53 (2 x H-C=, m), 5.77 (CH_2 , s), 6.07 (2 x H-C=, m).

15

EXAMPLE 5

Ethylene bis(chloromethyl carbonate)

- Pyridine (0.89 ml, 11.00 mmol) is added dropwise to a
20 solution of chloromethyl chloroformate (1.32 ml, 14.83 mmol) and ethylene glycol (0.28 ml, 5.00 mmol) in dichloromethane (10 ml) at 7°C with good stirring under a dry N_2 atmosphere. After 15 min. at 7°C and 6 hours at 20°C the reaction mixture is transferred to a separating
25 funnel with the aid of dichloromethane (10 ml). The reaction mixture is washed with hydrochloric acid (1.00 M, 10 ml), saturated aqueous sodium hydrogen carbonate (10 ml) and water (10 ml). The organic phase is dried ($MgSO_4$) and the solvent evaporated under reduced pressure
30 to give 1.12g (90%) of the title product. 1H NMR (300 MHz, $CDCl_3$): δ 4.48 (s, O- CH_2 CH₂-O), 5.75 (s, 2 x Cl- CH_2 -O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.8 (O- CH_2 CH₂-O), 72.2 (2 x Cl- CH_2 -O), 153.0 (2 x C=O).

35

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EXAMPLE 6

Bis(2-chloromethoxycarbonyloxyethyl)ether

Pyridine (0.89 ml, 11.00 mmol) is added dropwise to a
5 solution of chloromethyl chloroformate (1.32 ml, 14.83
mmol) and diethylene glycol (0.47 ml, 5.00 mmol) in
dichloromethane (10 ml) at 7°C with good stirring under
a dry N₂ atmosphere. After 10 min. at 7°C and 6 hours at
20°C the reaction mixture is transferred to a separating
10 funnel with the aid of dichloromethane (10 ml). The
reaction mixture is washed with hydrochloric acid (1.00
M, 10 ml), saturated aqueous sodium hydrogen carbonate
(10 ml) and water (10 ml). The organic phase is dried
(MgSO₄) and the solvent evaporated under reduced pressure
15 (10 mm Hg) to give 1.26 g (86%) title product. ¹H NMR
(300 MHz, CDCl₃): δ 3.72 (m, 2 x CH₂-O), 4.34 (m, 2 x
CH₂-O-C=O), 5.71 (s, 2 x Cl-CH₂-O). ¹³C NMR (75 MHz,
CDCl₃): δ 67.6 (2 x CH₂-O), 68.5 (2 x CH₂-O-C=O), 72.1 (2
x Cl-CH₂-O), 153.2 (2 x C=O).

20

EXAMPLE 7

1-Chloroethyl 2-methacryloyloxyethyl carbonate

25 Pyridine (0.89 ml, 11.00 mmol) is added dropwise to a
solution of 1-chloroethyl chloroformate (1.20 ml, 11.00
mmol) and 2-hydroxyethyl methacrylate (1.22 ml, 10.00
mmol) in dichloromethane (12 ml) at 3°C under a dry N₂
atmosphere. After 15 min. at 3°C and 17 hours at 20°C
30 the reaction mixture is transferred to a separating
funnel with the aid of dichloromethane (10 ml). The
reaction mixture is washed with hydrochloric acid (1.00
M, 10 ml), saturated aqueous sodium hydrogen carbonate
(10 ml) and water (2 x 10 ml). The organic phase is
dried (MgSO₄) and the solvent evaporated under reduced
35 pressure to give 1.76g (74%) of the title product. ¹H
NMR (60 MHz, CDCl₃): δ 1.85 (3 H, d, J=6 Hz, CH₃-CH),

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1.96 (3 H, d, J=2 Hz, CH₃-C=), 5.55 (1 H, m, CH=), 6.10 (1 H, m, CH=), 6.38 (1 H, k, J=6 Hz, CH-CH₃).

5 EXAMPLE 8

Chloromethyl 4-acryloyloxybutyl carbonate

Pyridine (0.89 ml, 11.00 mmol) is added dropwise to a solution of chloromethyl chloroformate (0.98 ml, 11.00 mmol) and 4-hydroxybutyl acrylate (1.38 ml, 10.00 mmol) in dichloromethane (12 ml) at 3°C under a dry N₂ atmosphere. After 15 min. at 3°C and 17 hours at 20°C the reaction mixture is transferred to a separating funnel with the aid of dichloromethane (10 ml). The reaction mixture is washed with hydrochloric acid (1.00 M, 10 ml), saturated aqueous sodium hydrogen carbonate (10 ml) and water (2 x 10 ml). The organic phase is dried (MgSO₄) and the solvent evaporated under reduced pressure to give 1.76g (74%) of the title product. ¹H NMR (60 MHz, CDCl₃): δ 1.82 (4 H, m, CH₂-CH₂), 4.27 (4 H, m, 2 x CH₂-O), 5.77 (2 H, s, Cl-CH₂-O), 5.8-6.7 (3 H, m, CH=CH₂).

25 EXAMPLE 9

1-Chloroethyl 4-acryloyloxybutyl carbonate

Pyridine (0.89 ml, 11.00 mmol) is added dropwise to a solution of 1-chloroethyl chloroformate (1.20 ml, 11.00 mmol) and 4-hydroxybutyl acrylate (1.38 ml, 10.00 mmol) in dichloromethane (12 ml) at 3°C under a dry N₂ atmosphere. After 15 min. at 3°C and 17 hours at 20°C the reaction mixture is transferred to a separating funnel with the aid of dichloromethane (10 ml). The reaction mixture is washed with hydrochloric acid (1.00 M, 10 ml), saturated aqueous sodium hydrogen carbonate (10 ml) and water (2 x 10 ml). The organic phase is

- 20 -

dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give 2.26g (90%) of the title product. 1H NMR (60 MHz, $CDCl_3$): δ 1.80 (4 H, m, CH_2-CH_2), 1.86 (3 H, d, $J=5$ Hz, CH_3), 4.24 (4 H, m, 2 \times CH_2-O), 5.7-6.6 (4 H, s, $CH=CH_2$ and CH).

EXAMPLE 10

1-Methacryloyloxyethyl 2-methacryloyloxyethyl carbonate

10 1-Chloroethyl 2-methacryloyloxyethyl carbonate (1.183g, 5.00 mmol) prepared as described in Example 7 is added to a suspension of freeze dried potassium methacrylate (0.683 g, 5.50 mmol) and 18-crown-6 (0.066 g, 0.25 mmol) 15 in dimethylformamide (50 ml) under a dry N_2 atmosphere. After 5 days at 20°C the solvent is removed under reduced pressure and the residue dissolved by adding dichloromethane (60 ml) and water (30 ml). After separating the phases the aqueous layer is extracted 20 with dichloromethane (3 \times 30 ml) and the combined organic phase washed with saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase is dried ($MgSO_4$) and the solvent removed under reduced pressure to give 1.10g (77%) of the title product. 1H NMR (60 MHz, $CDCl_3$): δ 1.63 (3 H, d, $J=5$ Hz, CH_3-CH), 1.98 (6 H, s, 2 \times CH_3), 4.42 (4 H, s, 0- CH_2-CH_2-O), 5.62 (2 H, m, $CH=$), 25 6.15 (2 H, m, $CH=$), 6.84 (1 H, k, $J=5$ Hz, $CH-CH_3$).

30 EXAMPLE 11

Acryloyloxymethyl 4-acryloyloxybutyl carbonate

Chloromethyl 4-acryloyloxybutyl carbonate (1.183g, 5.00 mmol) prepared as described in Example 8 is added to a 35 suspension of freeze dried potassium acrylate (0.606 g, 5.50 mmol) and 18-crown-6 (0.066 g, 0.25 mmol) in dimethylformamide (50 ml) under a dry N_2 atmosphere.

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After 5 days at 20°C the solvent is removed under reduced pressure and the residue dissolved by adding dichloromethane (60 ml) and water (30 ml). After separating the phases the aqueous layer is extracted
5. with dichloromethane (3 x 30 ml) and the combined organic phase washed with saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase is dried ($MgSO_4$) and the solvent removed under reduced pressure to give 1.24g (91%) of the title product. 1H NMR (60 MHz,
10 $CDCl_3$): δ 1.82 (4 H, m, CH_2-CH_2), 4.23 (4 H, m, 2 x CH_2-O), 5.88 (2 H, s, O- CH_2-O), 5.7-6.8 (6 H, 2 x $CH=CH_2$).

EXAMPLE 12

15 1-Acryloyloxyethyl 4-acryloyloxybutyl carbonate

1-Chloroethyl 4-acryloyloxybutyl carbonate (1.253g, 5.00 mmol) prepared as described in Example 9 is added to a suspension of freeze dried potassium acrylate (0.606 g, 20 5.50 mmol) and 18-crown-6 (0.066 g, 0.25 mmol) in dimethylformamide (50 ml) under a dry N_2 atmosphere. After 5 days at 20°C the solvent is removed under reduced pressure and the residue dissolved by adding dichloromethane (60 ml) and water (30 ml). After separating the phases the aqueous layer is extracted
25 with dichloromethane (3 x 30 ml) and the combined organic phase washed with saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase is dried ($MgSO_4$) and the solvent removed under reduced pressure to give 1.28g (89%) of the title product. 1H NMR (60 MHz,
30 $CDCl_3$): δ 1.58 (3 H, d, J=5 Hz, CH_3-CH), 1.80 (4 H, m, CH_2-CH_2), 4.24 (4 H, m, 2 x CH_2-O), 5.7-6.7 (6 H, m, 2 x $CH=CH_2$), 6.87 (1 H, k, J=5 Hz, $CH-CH_3$).

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EXAMPLE 13

Methylene bis(p-vinylbenzoate)

Diiodomethane (0.20 ml, 2.50 mmol) is added to a
5 solution of freeze dried potassium p-vinylbenzoate
(0.931 g, 5.00 mmol), 18-crown-6 (0.040 g, 0.25 mmol)
and hydroquinone (0.011 g, 0.10 mmol) in
dimethylformamide (35 ml) under a dry N₂ atmosphere and
the reaction mixture left for 2.5 days at 60°C. The
10 solvent is removed under reduced pressure and the
residue dissolved by adding diethyl ether (20 ml),
saturated aqueous sodium hydrogen carbonate (5 ml) and
water (10 ml). After separating the phases the aqueous
layer is extracted with diethyl ether (6 x 10 ml) and
15 the combined organic phase washed with water (5 x 10
ml). The organic phase is dried (MgSO₄) and the solvent
removed under reduced pressure to give 0.64g (83%) of
the title product. ¹H NMR (300 MHz, CDCl₃): δ 5.39 (2 H,
d, J=10 Hz, 2 x CH=), 5.86 (2 H, d, J=17.6 Hz, 2 x CH=),
20 6.24 (2 H, s, O-CH₂-O), 6.73 (2 H, dd, J=11.0, 17.6, 2 x
CH=), 7.45 (4 H, 2 x d, J=6.8 Hz, Ar), 8.04 (2 H, d,
J=6.6 Hz, Ar), 8.05 (2 H, d, J=6.6 Hz, Ar). ¹³C NMR (75
MHz, CDCl₃): δ 79.8 (O-CH₂-O), 116.8 (2 x CH=), 126.0,
130.2 (C₂, C₂', C₃; C₃'), 127.8, 142.5 (C₁, C₁', C₄, C₄'), 135.7
25 (2 x CH=), 164.9 (2 x C=O).

EXAMPLE 14

Methylene bis(p-bromobenzoate)

30 Diiodomethane (0.60 ml, 7.50 mmol) is added to a
solution of freeze dried potassium p-bromobenzoate
(3.587 g, 15.00 mmol) and 18-crown-6 (0.198 g, 0.75
mmol) in dimethylformamide (100 ml) under a dry N₂
atmosphere and the reaction mixture left for 4 days at
35 60°C. The solvent is removed under reduced pressure and
the residue dissolved by adding dichloromethane (60 ml)

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and water (30 ml). After separating the phases the aqueous layer is extracted with dichloromethane (3 x 30 ml) and the combined organic phase washed with saturated aqueous sodium hydrogen carbonate (50 ml). The organic phase is dried ($MgSO_4$) and the solvent removed under reduced pressure to give 2.62g (84%) of the title product. 1H NMR (60 MHz, $CDCl_3$): δ 6.29 (2 H, s, $O-CH_2-O$), 7.63 (4 H, d, $J=9$ Hz, Ar), 8.00 (4 H, d, $J=9$ Hz, Ar).

10

EXAMPLE 15

Methylene bis(p-hydroxybenzoate)

15 Diiodomethane (0.40 ml, 5.00 mmol) is added to a solution of freeze dried potassium p-hydroxybenzoate (1.762 g, 10.00 mmol) in dimethylformamide (60 ml) under a dry N_2 atmosphere and the reaction mixture left for 4 days at 60°C. The solvent is removed under reduced pressure and the residue dissolved by adding dichloromethane (60 ml) and water (30 ml). After separating the phases the aqueous layer is extracted with dichloromethane (3 x 30 ml) and the combined organic phase washed with brine (50 ml). The organic phase is dried ($MgSO_4$) and the solvent removed under reduced pressure to give 0.94g (65%) of the title product. 1H NMR (60 MHz, $CDCl_3/CD_3OD$ 1:2): δ 4.92 (2 H, s, 2 x OH), 6.18 (2 H, s, $O-CH_2-O$), 6.88 (4 H, d, $J=9$ Hz, Ar), 7.96 (4 H, d, $J=9$ Hz, Ar).

20

EXAMPLE 16

Methylene bis[p-(hydroxymethylethynyl)benzoate]

35 Bis (triphenylphosphine)palladium dichloride (17.0 mg, 0.02 mmol) and cuprous iodide (2.0 mg, 0.01mmol) are added to a suspension of methylene bis (p-bromobenzoate)

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(0.500 g, 1.21 mmol) prepared as described in Example 14 and propargyl alcohol (0.16 ml, 2.66 mmol) in triethylamine (10 ml) with good stirring, at 20°C, under a dry N₂ atmosphere. After 10 days at 20°C, the
5 triethylamine is removed under reduced pressure, water (20 ml) is added and the mixture is extracted with dichloromethane (3 x 15 ml). The dichloromethane phases are washed with hydrochloric acid (0.5 M, 10 ml), dried (MgSO₄) and the dichloromethane removed under reduced
10 pressure to give 0.37 g (85%) of the crude product. ¹H NMR (60 MHz, CDCl₃): δ 3.67 (2 H, s, OH), 4.47 (4 H, s, CH₂-O), 6.18 (2 H, s, O-CH₂-O), 7.2-7.5 (4 H, Ar), 7.8-
8.0 (4 H, Ar).

15

EXAMPLE 17

Adipic acid bis (1-chloroethyl ester)

Anhydrous zinc chloride (10.0 mg, 0.07 mmol) is added to
20 adipoyl chloride (2.92 ml, 20.00 mmol) at 20°C, under a dry N₂ atmosphere. Acetaldehyde (2.26 g, 40.00 mmol) is added dropwise to the reaction mixture at -5°C. The reaction temperature is kept between -5°C and 0°C and dichloromethane (20 ml) is added. The zinc chloride
25 catalyst is removed by passing the reaction mixture through a chromatography column containing aluminium oxide (Fluka 06290, type 5016 A basic, 20 g) at 5°C using dichloromethane as the solvent. The solvent is removed under reduced pressure to give 3.64 g (67%) of
30 the crude product. ¹H NMR (60 MHz, CDCl₃): δ 1.5-1.9 (4 H, m, CH₂-CH₂), 1.77 (6 H, d, J=6 Hz, 2 x CH₃), 2.1-2.5 (4 H, m, 2 x CH₂-O), 6.49 (2 H, k, J=6 Hz, 2 x Cl-CH-O).

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EXAMPLE 18

Methylene bis [p-(2,3-epoxy-1-propyloxy)benzoate]

Potassium tert.butoxide (1.347 g, 12.00 mmol) is added
5 to a solution of methylene di(p-hydroxybenzoate) (1.728
g, 6.00 mmol) prepared as described in Example 15 in DMF
(75 ml), under a dry N₂ atmosphere. Epichlorohydrin
(2.22 g, 24.00 mmol) is added and after 24 hours at 20°C
the solvent is removed under reduced pressure. The
10 residue is dissolved by adding dichloromethane (75 ml)
and water (30 ml) and adjusting the pH to neutral using
hydrochloric acid (1 M). After separating the phases
the dichloromethane layer is washed with water (3 x 30
ml). The organic phase is dried (MgSO₄) and the solvent
15 removed under reduced pressure to give 1.22 g (51%).
product as a colourless oil. ¹H NMR (60 MHz, CDCl₃): δ
2.8 (4 H, m, 2 x epoxy-CH₂), 3.3 (2 H, m, 2 x epoxy-CH),
4.05 (2 H, dd, J=22, 11 Hz, 2 x O-CH-H), 4.12 (2 H, dd,
J=22, 11 Hz, 2 x O-CH-H), 6.14 (2 H, s, O-CH₂-O), 6.9 (4
20 H, m, 2 x Ar), 7.9 (4 H, m, 2 x Ar).

EXAMPLE 19

Methylene bis(3,3-dimethoxypropionate)

Cesium 3,3-dimethoxypropionate (19.95 g, 75 mmol) is
25 added to dry DMF (1000 ml). Diiodomethane (10.04 g,
37.5 mmol) is added to the suspension and the reaction
mixture is stirred for 2 days at 60°C under a dry N₂
atmosphere. DMF is removed under reduced pressure (0.01
mmHg). Diethyl ether (500 ml) is added to the residue,
30 which is then washed with saturated aqueous sodium
hydrogen carbonate (250 ml). The aqueous layer is
extracted with diethyl ether (5 x 75 ml). The combined
ether extracts are washed with water (2 x 100 ml), dried
35 (MgSO₄) and evaporated to give 7.1 g (72%) product. ¹H
NMR (300 MHz, CDCl₃): δ 2.61 (CH₂, d), 3.26 (CH₃, s),

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HC=, m). ^{13}C NMR (300 MHz, CDCl_3): δ 24.92-33.98 (8 x CH_2), 79.04 ($\text{O}-\text{CH}_2-\text{O}$), 114.18 (= CH_2), 139.11 (= CH), 172.48 (C=O).

5

EXAMPLE 22

Methylene bis(10-epoxyundecanoate)

Methylene bis(10-undecenoate) (8.8g, 25 mmol) prepared
as described in Example 21 is added under an N_2
atmosphere to methylene chloride and cooled to 0°C.
Metachloroperbenzoic acid 55t (15.75g, 50 mmol) is added
to methylene chloride (150 ml) and the organic layer is
separated and dried (MgSO_4). The metachloroperbenzoic
acid is then added dropwise to the diester. After
completed addition the temperature is increased to 25°C.
After 5 hours the reaction is complete. The mixture is
washed with saturated aqueous sodium sulphite (75 ml)
and saturated aqueous sodium hydrogen carbonate (2 x 75
ml). The organic layer is purified on neutral aluminium
oxide. The solvent is removed under reduced pressure to
yield 8.45g (82t) product. ^1H NMR (300 MHz, CDCl_3): δ
1.2-1.7 (14 x CH_2 , m), 2.35 (2 x $\text{CH}_2\text{CO}, \text{t}$), 2.45 (2 x CH, q),
2.75 (2 x CH, q), 2.90 (2 x CH, m), 5.75 ($\text{O}-\text{CH}_2-\text{O}$). ^{13}C
NMR (300 MHz, CDCl_3): δ 24.58 (CH_2), 25.99 (CH_2), 28.94
(CH_2), 29.09 (CH_2), 29.32 (2 x CH_2), 32.45 (CH_2), 33.92
(CH_2), 47.06 (CH_2-O), 52.36 ($\text{CH}-\text{O}$), 79.06 ($\text{O}-\text{CH}_2-\text{O}$),
172.2 (C=O).

30

EXAMPLE 23

Methylene bis(hydroxyacetate)

(a) Methylene bis(benzyloxyacetate)

35

Benzyl oxyacetic acid (49.8 g, 300 mmol) is dissolved in
a 500 ml mixture of water and MeOH (60:40), and cesium

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carbonate (48.9 g, 150 mmol) is added to the solution. The solvent is evaporated under reduced pressure and residual water is removed azeotropically with benzene. The salt is dissolved in 1500 ml DMF and diiodomethane 5 (40.2 g, 150 mmol) is added to the solution. The reaction mixture is stirred for 3 days at 60°C under an N₂ atmosphere. The DMF is removed under reduced pressure and the residue is dissolved in ether (250 ml) and washed with saturated aqueous sodium hydrogen carbonate 10 (250 ml) and water (3 x 75 ml) before drying (MgSO₄). The solvent is evaporated and the residue is purified through silica gel with hexane/ethyl acetate (7:3) as eluant to give 23.6 g (46%) product. ¹H NMR (300 MHz, CDCl₃): δ 4.1 (2 x CH₂, s), 4.6 (2 x CH₂, s), 5.9 (O-CH₂- 15 O, s), 7.35 (2 x C₆ H₅, m).

(b) Methylene bis(hydroxyacetate)

Methylene bis(benzyloxyacetate) (0.52 g, 1.5 mmol) and 20 Pd/C (100 mg, 10%) are added to dry ethanol (100 ml). Hydrogen (1 atm) is introduced and the reaction is complete after 16 hours at room temperature, whereupon the reaction mixture is filtered and the solvent is evaporated under reduced pressure (0.01 mmHg) to yield 25 0.23 g (95%) product. ¹H NMR (200 MHz, MeOH): δ 4.2 (CH₂, s), 4.9 (OH), 5.9 (OCH₂O, s). The product may be used to form polyesters with di- or poly- acids and to form polyurethanes with isocyanates.

30

EXAMPLE 24

Methylene bis(16-hydroxyhexadecanoate)

(a) 16-Triphenylmethoxyhexadecanoic acid

35

A solution of 16-hydroxyhexadecanoic acid (1.36 g, 5.00 mmol), triphenylmethyl chloride (1.53 g, 5.50 mmol), triethylamine (1.25 ml) and 4-dimethylaminopyridine

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(10.03 g, 0.25 mmol) is stirred overnight in dry dimethylformamide at ambient temperature under nitrogen.

After 16 hours stirring, the brown cloudy solution is poured into ice-water and extracted with dichloromethane

5 (5 X 50 ml). The organic phases are washed with saturated ammonium chloride solution (2 X 100 ml), water (2 X 100 ml) and dried over MgSO₄. The solvent is removed under reduced pressure and the product purified by flash chromatography on a silica column with

10 dichloromethane/methanol (20:1) as eluant to yield the title compound as a yellow oil (0.41 g). ¹³C NMR (75 MHz, CDCl₃): δ 24.9, 25.7, 26.3, 29.2, 29.5, 29.6, 29.7, 30.0, 32.8, 34.1, 62.9, 63.7, 86.2, 144.5, 177.2.

MS (CI): 515 (M + H)

15

(b) 16-Triphenylmethoxyhexadecanoic acid cesium salt

Aqueous cesium carbonate (1M, 0.16 ml) is added dropwise

20 to a solution of 16-triphenylmethoxyhexa-decanoic acid (0.16 g, 0.31 mmol) in tetrahydrofuran (10 ml) until the pH reaches approximately 8, whereupon the solvent is removed under reduced pressure and the residue dried under vacuum for 2 hours. The oily semicrystalline 25 residue is dispersed in dry dimethylformamide (10 ml) and evaporated to dryness in vacuo. The crystalline product is used without further characterization.

(c) Methylene bis(16-triphenylmethoxyhexadecanoate)

30

Diodomethane (0.04 g, 0.16 mmol) is added to a suspension of 16-triphenylmethoxyhexadecanoic acid cesium salt (0.31 mmol) in dry dimethylformamide (10 ml). The reaction mixture is heated at 60 °C for 2 days 35 under nitrogen. The solvent is removed in vacuo, and the product purified by flash chromatography on a 2 x 5 cm silica column with chloroform as eluant to yield the title compound as a brown oil (0.10 g). ¹³C NMR (75 MHz,

- 30 -

CDCl₃): δ 24.6, 26.3, 29.0, 29.2, 29.4, 29.5, 29.6, 29.7, 30.0, 34.0, 63.7, 79.0, 86.2, 126.7, 127.2, 127.6, 127.9, 128.7, 144.5, 172.5.

5 (d) Methylene bis(16-hydroxyhexadecanoate)

Methylene bis(16-triphenylmethoxyhexadecanoate) (0.07g, 0.07 mmol) is dissolved in glacial acetic acid (8 ml) and heated at 55°C. The reaction is monitored by TLC.
10 After 10 hours the reaction mixture is poured onto ice, and the crude product is filtered, washed with aqueous sodium bicarbonate and water, and dried under reduced pressure. The product is purified by flash chromatography on a silica column with chloroform/methanol (20:1) as eluant to yield the title compound as a white solid. ¹H-NMR (300 MHz, CDCl₃): δ 1.2-1.4(m, 4H), 1.5-1.6(m, 8H), 2.35(t, 4H), 3.64(t, 4H), 5.75(s, 2H).

20

EXAMPLE 25

Methylene bis(hydrogen azelate)

(a) Benzyl hydrogen azelate

25

Toluene-4-sulfonic acid monohydrate (0.71 g, 3.72 mmol) is added to a suspension of azelaic acid (25.0 g, 132.82 mmol) in benzene (550 ml). The mixture is heated to 80°C, whereafter benzyl alcohol (14.36 g, 132.82 mmol) in benzene (50 ml) is added dropwise to the resulting solution. The reaction mixture is refluxed overnight and water is removed azeotropically with a Dean Stark trap. The reaction mixture is allowed to cool, the white precipitate which forms is removed by filtration and the filtrate is concentrated to a brownish oil under reduced pressure. The crude product (33.97 g) is dissolved in dichloromethane (50 ml) and purified by flash chromatography on a 5.5 x 15 cm silica column with

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dichloromethane/methanol (20:1) as eluant. The product, a yellow oil, is dried under vacuum. The oil crystallizes after a few hours at room temperature.

Yield: 12.8 g (35%). ^{13}C NMR (75 MHz, CDCl_3): δ 24.5,

- 5 24.8, 28.8, 34.0, 34.2, 66.1, 128.2, 128.5, 136.1,
173.6, 180.0.

(b) Cesium benzyl azelate

- 10 Aqueous cesium carbonate (1M, 6.3 ml) is added dropwise to a solution of benzyl hydrogen azelate (3.00 g, 10.77 mmol) in 75 ml water/methanol (1:15) until the pH reaches approximately 7, whereupon the solvent is removed under reduced pressure and the residue dried
15 under vacuum overnight. The oily, yellowish semicrystalline residue is dispersed in dry dimethylformamide (50 ml) and evaporated to dryness in vacuo. This procedure is repeated twice, yielding an off-white crystalline product. The product is used
20 without further characterization.

(c) Methylene bis(benzyl azelate)

- 25 Diiodomethane (1.44 g, 5.37 mmol) is added to a suspension of cesium benzyl azelate (4.41 g, 10.77 mmol) in dry dimethylformamide (75 ml) under nitrogen. The reaction mixture is heated at 60°C for 2 days, whereafter the solvent is removed under reduced pressure and the residue is transferred to an extraction funnel
30 with ethyl acetate (150 ml) and water (75 ml). The organic phase is extracted with water (3x50 ml), dried over MgSO_4 , and concentrated to a yellow oil in vacuo. Yield: 2.86 g (95.6%). ^{13}C NMR (75 MHz, CDCl_3): δ 24.4,
24.8, 28.7, 28.8, 28.9, 33.8, 34.2, 66.0, 79.0, 128.1,
35 128.5, 136.1, 172.3, 173.5.

(d) Methylene bis(hydrogen azelate)

- 32 -

Methylene bis(benzyl azelate) (10 g, 17.58 mmol) is dissolved in glacial acetic acid (250 ml). 10% Pd/C (2.0 g) is added, and hydrogen gas is bubbled through the solution for 2 hours. The reaction is monitored by 5 TLC. The catalyst is removed by filtration and the solvent is removed under reduced pressure. The crude product is dissolved in diethyl ether and petroleum ether is added. An oil precipitates, which crystallizes after 1 hour. The mixture is left in a refrigerator 10 overnight before the crystals are collected by filtration and dried under vacuum, to yield the title compound. Yield: 5.33 g (78%). ^{13}C NMR (75 MHz, CDCl_3): δ 24.5, 24.6, 28.7, 28.8, 33.9, 79.1, 172.5, 180.0. mp: 57-60°C.

15

EXAMPLE 26

Methylene bis(hydrogen tetracosanedioate)

20 (a) Benzyl hydrogen tetracosanedioate

Toluene-4-sulfonic acid monohydrate (0.05 g, 0.28 mmol) is added to a suspension of tetracosanedioic acid (5.0 g, 80%, 10.03 mmol) in benzene (180 ml). The mixture is 25 heated to 80°C, whereafter benzyl alcohol (1.08 g, 10.03 mmol) in benzene (10 ml) is added dropwise to the resulting solution. The reaction mixture is refluxed for 20 hours and water is removed azeotropically with a Dean Stark trap. The solvent is removed under reduced 30 pressure and the residue washed with petroleum ether. The product is dissolved in refluxing diethyl ether and purified by flash chromatography on a silica column with methylene chloride/methanol (20:1) as eluant to yield the title compound as a white crystalline solid. ^{13}C NMR (75 MHz, CDCl_3): δ 24.0, 28.5, 29.7, 30.9, 34.4, 66.2, 128.2, 128.5, 136.0, 174.1, 176.9.

(b) Methylene bis(hydrogen tetracosanedioate)

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The product from (a) above is reacted in similar manner to that described in Example 25 (b)-(d) to yield the title compound.

5

EXAMPLE 27

Methylene bis(4-pentenoate)

10 4-Pentenoic acid (10g, 100 mmol), diiodomethane (13.4 g, 50 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (15.25 g, 100 mmol) are dissolved in acetonitrile (150 ml). The solution is refluxed under nitrogen for 3 hrs, whereafter acetonitrile is removed under reduced pressure. The residue is dissolved in water (75 ml) and extracted with diethyl ether (3x 100 ml). The combined ether extracts are washed with saturated aqueous sodium carbonate (50 ml), dried (MgSO_4) and evaporated to give 8.39 g (79%) product. ^{13}C NMR (75 MHz, CDCl_3): δ 28.48 (2x CH_2), 33.20 (2x CH_2), 79.11 ($\text{O}-\text{CH}_2-\text{O}$), 115.80 (2x $\text{H}_2\text{C}=\text{}$), 136.18 (2x = $\text{CH}-$), 171.68 (2x C=O).

25

EXAMPLE 28

Methylene bis(4-époxypentanoate)

Metachloroperbenzoic acid (15.68 g, 55%, 50 mmol) is dissolved in methylene chloride (200 ml). Water is separated and the organic layer is dried (MgSO_4). The resulting metachloroperbenzoic acid solution is added dropwise to methylene bis(4-pentenoate) (4.10 g, 19 mmol) dissolved in methylene chloride (50 ml). The mixture is stirred at ambient temperature under nitrogen for 12 hrs, whereafter the reaction mixture is washed with saturated aqueous sodium bicarbonate solution (50 ml), water (50 ml), dried (MgSO_4) and evaporated to give 3.61g (78%) of the title compound as a crystalline product. ^1H NMR (300 MHz, CDCl_3): δ 1.70-1.85 (2x CH , m), 1.95-2.10 (2x CH , m), 2.50-2.55 (2x CH , 2x CH_2 , m), 2.75

- 34 -

(2xCH,t), 3.0 (2xCH,m), 5.8 (O-CH₂-O, s). ¹³C NMR (75 MHz, CDCl₃): δ 27 (2xCH₂), 30 (2xCH₂), 47 (2xCH₂), 51 (2xCH), 79.8 (O-CH₂-O), 171.8 (2xC=O).

5

EXAMPLE 29

Methylene bis(2-butenoate)

Vinylacetic acid (4.3 g, 50 mmol) is added to an aqueous
10 cesium carbonate solution (50 ml). The mixture is
stirred for 5 min. and then evaporated, and the residue
is dried under vacuum for 2 hrs. The resulting cesium
salt and diiodomethane are added to dimethylformamide
15 (200 ml) and the mixture is stirred for 24 hrs. at 50°C
under nitrogen, whereafter the dimethylformamide is
removed under reduced pressure. The residue is
dissolved in diethyl ether (100 ml) and washed with
saturated aqueous sodium bicarbonate (25 ml) and water
(25 ml). The organic layer is dried (MgSO₄) and
20 evaporated to give 1.32 g (29%) product. ¹H NMR (300
MHz, CDCl₃): δ 1.9 (2xCH₂,m), 5.8-5.9 (2xCH,m), 5.9
(OCH₂O,s), 7.0-7.1 (2xCH,m).

25

EXAMPLE 30

Methylene bis(chloroacetate)

Chloroacetic anhydride (12.75 g, 75 mmol),
paraformaldehyde (2.25 g, 75 mmol) and conc. sulfuric
30 acid (15 drops) are added to methylene chloride (15 ml).
The mixture is stirred for 24 hrs. at 50°C under
nitrogen, whereafter the reaction mixture is extracted
with saturated aqueous potassium carbonate until carbon
dioxide emission ends. The organic layer is dried
35 (MgSO₄), evaporated to dryness and the residue is
distilled (80°C, 0.15 mmHg) to yield 10.2 g (57%)
product. ¹H NMR (200 MHz, CDCl₃): δ 4.1 (2xCH₂Cl,s), 5.9
(CH₂,s). ¹³C NMR (200 MHz, CDCl₃): δ 41.1 (CH₂Cl), 81.4

- 35 -

(O-CH₂-O), 166.4 (CO).

EXAMPLE 31

5 Methylene bis(4-oxopentanoate)

4-Oxopentanoic acid (11.6 g, 100 mmol) is dissolved in acetonitrile (70 ml), and 1,8-diazabicyclo[5.4.0]undec-7-ene (15.25 g, 100 mmol) diluted with acetonitrile (30 ml) is added. Diiodomethane (13.4 g, 50 mmol) is added in one batch, and the reaction mixture is refluxed under a nitrogen atmosphere. After 2 hours, gas chromatography indicates full consumption of diiodomethane. The solvent is removed in vacuo and the residual brown oil is transferred to a separation funnel with ethyl acetate (200 ml) and water (75 ml). The organic phase is washed with 1M sodium bicarbonate (25 ml) and water (3 x 25 ml), dried over MgSO₄, and the solvent is removed in vacuo to yield the title compound (10 g). ¹H NMR: δ 2.19 (2 x CH₃, s), 2.760-2.804 (2 x CH₂, t), 2.600-2.645 (2 x CH₂, t), 5.735 (CH₂ bridge, s).

EXAMPLE 32

25 Methylene bis(hydrogen glutarate)

(a) Benzyl hydrogen glutarate

A suspension of glutaric anhydride (50 g, 430 mmol) in benzyl alcohol (54 g, 500 mmol) is heated at 105°C overnight, whereafter gas chromatography indicates full consumption of the anhydride. Purification of a 1.3g sample by flash chromatography on a 2.5 X 15 cm silica column with chloroform and methanol/chloroform (1:10) as eluants yields title compound (1.1 g). ¹H NMR: δ 1.945-1.993 (CH₂, m), 2.397-2.470 (2x CH₂, m), 5.117 (CH₂, s), 7.332-7.357 (C₆H₅, m). The remaining crude product is purified by short path distillation; the main fraction

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is collected at 150 - 160°C/0.04 mmHg. Yield: 90 g.

(b) Cesium benzyl glutarate

5 Crude benzyl hydrogen glutarate (25 g, 100 mmol) is stirred in water (100 ml) to form a slurry. An aqueous solution of 1 M cesium carbonate is added until the pH reaches 7 (52 ml is consumed). The homogeneous reaction mixture is diluted with water (150 ml), and extracted
10 with chloroform (2 x 50 ml) to remove nonpolar impurities from the crude starting material. Water is removed in vacuo, and the oily, grayish semicrystalline residue is slurried in dimethylformamide (200 ml), and evaporated to dryness in vacuo. This procedure is
15 repeated twice, yielding an off-white crystalline product, which is used without further characterization.

(c) Methylene bis(benzyl glutarate)

20 Cesium benzyl glutarate (100 mmol) is slurried in dimethylformamide (150 ml). Diiodomethane (13.4 g, 50 mmol) is added, and the reaction mixture is heated at 70°C overnight under a nitrogen atmosphere. The resulting reaction mixture is a dark, brownish slurry,
25 which is rendered homogeneous by addition of water (50 ml). The solvent is removed in vacuo, and the residue is transferred to an extraction funnel with ethyl acetate (200 ml) and water (100 ml). The organic phase is extracted with water (2 x 50 ml), dried over MgSO₄, and concentrated in vacuo to a brownish oil (15.5 g).
30 0.5 g of this product is purified by flash chromatography on a 2.5 x 15 cm silica column with methylene chloride and methanol/chloroform (1:10) as eluants to yield the title compound. ¹H NMR (300 MHz, CDCl₃): δ 1.94-1.99 (2 x CH₂, q), 2.40-2.44 (4 x CH₂, t), 5.11 (2 x CH₂, s), 5.28 (CH₂ bridge, s), 7.33-7.35 (2 x C₆H₅, m).

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The main part of the product is used without further purification.

(d) Methylene bis(hydrogen glutarate)

5

Crude methylene bis(benzyl glutarate) (10 g, 22 mmol) is dissolved in a mixture of acetic acid (50 ml) and tetrahydrofuran (25 ml). 10% Pd/C (1.5 g) is added, and hydrogen gas is bubbled through the solution for 3h. The reaction is monitored by TLC. The catalyst is removed by filtration and the solvent is removed in vacuo. The crude product is dissolved in diethyl ether and hexane is added. An oil precipitates. After a few hours in a refrigerator, the oil crystallizes. The crystals are collected by filtration and dried under vacuum. Yield: 15 5g (80%). ^{13}C NMR (75 MHz, CDCl_3): 171.627 ppm (CO-bridge), and 179.198 ppm (CO-free acid).

EXAMPLE 33

20 Methylene bis(succinimidylazelate)

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.49 g, 7.71 mmol) was added in portions to a stirred solution of methylene bis(hydrogen azelate) from Example 25 (1.00 g, 2.57 mmol) and N-hydroxysuccinimide (0.89 g, 7.71 mmol) in dry dimethylformamide at ambient temperature. After 20 hours stirring, the reaction mixture was poured into ice-water, whereupon the product precipitated as an oil. 30 The colourless oil was dissolved in diethylether (50 ml), washed with water (3x10 ml) and dried over MgSO_4 . The solvent was removed under reduced pressure and hexane (5 ml) was added to the oily product. After seven days storage at 4°C the oil had crystallized to a white, waxy solid. Yield: 1.50 g (69%). m.p.: 45-47°C. ^{13}C NMR (75 MHz, CDCl_3): δ 24.42, 24.46, 25.59, 28.48, 28.63, 30.85, 33.82, 79.61, 168.6, 169.30, 172.34.

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EXAMPLE 34

Methylene bis(16-acryloyloxyhexadecanoate)

5 Triethylamine (0.29 g, 2.87 mmol) in dry toluene (2 ml) was added to a suspension of methylene bis(16-hydroxydecanoate) from Example 24 (0.20 g, 0.36 mmol) in dry toluene (5 ml). The mixture was heated to 50°C under nitrogen and acryloylchloride (0.26 g, 2.87 mmol) in dry toluene (3 ml) was then added dropwise. After 1 hour of stirring at 55°C the reaction mixture was cooled to room temperature, diluted with toluene (10 ml), washed with water (2x5 ml) and dried over MgSO₄. The solvent was evaporated under reduced pressure to give a yellow solid product. Yield: 0.2 g (92%). MS (CI): 665 (M + H). ¹³C NMR (75 MHz, CDCl₃): δ 24.62, 25.93, 28.62, 29.01, 29.24, 29.26, 29.45, 29.52, 29.58, 29.60, 29.64, 33.98, 64.72, 78.99, 128.64, 130.43, 166.33, 172.52.

20 EXAMPLE 35

Methylene bis(10-methyl-6,8-dioxa-5,7-dioxoundecanoate)

25 Methylene bis(hydrogen glutarate) (1 g, 3.6 mmol) is dissolved in 25 ml dry acetone.. Triethylamine (1 ml, 7.2 mmol) is added, and the reaction mixture is cooled to 0°C. Isobutylchloroformate (0.99 ml, 7.2 mmol) is added. The cooling bath is removed after 1 hour and stirring is continued for 1 hour. The reaction mixture is filtered and the solvent is removed in vacuo. The 30 product is characterised by NMR, and is used without further purification.

EXAMPLE 36

35 Methylene bis(4-fluorocarbonyl)butyrate

Methylene bis(hydrogen glutarate) (1 g, 3.6 mmol) is reacted with cyanuric fluoride as described by Olah et

- 39 -

al., Synthesis (1973) 487-488. The product is characterised by NMR and used without further purification.

5

EXAMPLE 37

Methylene bis(10-oxodecanoate)

a) Methylene bis(10,11-dihydroxyundekanoate)

5 N-Methylmorpholine-N-oxide (13.5 g, 11 mmol) and methylene bis(10-undecenoate) from Example 21 (19 g, 5 mmol) were dissolved in 400 ml of a mixture of tetrahydrofuran and water (3:1 v/v). A catalytic amount of osmium tetroxide was added, and the solution stirred
10 at ambient temperature for 20 hours. TLC indicated complete consumption of the starting material. Excess sodium hydrogen sulphite and sodium chloride were then added to the reaction mixture. The product was extracted from the resulting mixture with ethyl acetate
15 (400 ml) and the water phase was washed with ethyl acetate (3 x 50 ml). The combined organic phases were dried and evaporated, and the product recrystallised from tetrahydrofuran to yield 14.5g (68%) of the product as a white solid. ^{13}C NMR (45 MHz) CD_3OD : δ 24.6-34.0 (16 x CH_2), 66.6 (2 x CH_2OH), 72.3 (2 x CHOH) 79.2 ($\text{O}-\text{CH}_2-\text{O}$), 174.0 (2 x C=O).

b) Methylene bis(10-oxodecanoate)

25 Methylen bis(10,11-dihydroxyundekanoate) (2.24 g, 5 mmol) was dissolved in 150 ml tetrahydrofuran. Sodium metaperiodate (2.06 g, 10 mmol) was dissolved in 150 ml water and added dropwise to the tetrahydrofuran solution. TLC indicated full consumption of the diol
30 after 60 minutes, whereupon sodium chloride was added to the reaction mixture until the two phases separated. The water phase was extracted with diethyl ether (3 X 50

- 40 -

ml). The combined organic phases were dried with magnesium sulphate and evaporated to give the title product as an oil, 1.43 g (74%). ^{13}C NMR (45 MHz) CDCl_3 : δ 21.9-43.9 (16 x CH_2), 79.1 ($\text{O}-\text{CH}_2-\text{O}$), 173.0 (2 x C=O), 5 202.6 (2 x CHO).

EXAMPLE 38

Methylene bis(sulphosuccinimidylazelate) sodium salt

10

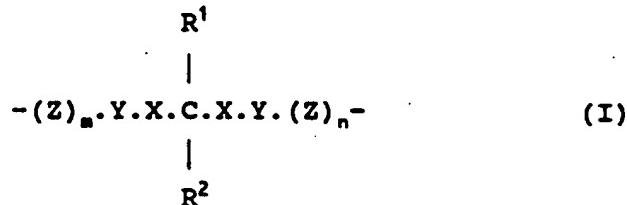
Methylene bis(hydrogen azelate) (0.38 g, 1 mmol), N-hydroxysulphosuccinimide sodium salt (0.48 g, 2.2 mmol) and dicyclohexylcarbodiimide (0.45 g, 2.2 mmol) was dissolved in dimethylformamide (10 ml). The suspension 15 was stirred overnight at room temperature under a nitrogen atmosphere. The reaction mixture was filtered and purified by reversed phase chromatography (RP-8) with water/acetonitrile (1:1) as eluant to give the title compound.

20

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CLAIMS

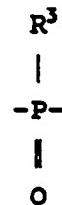
- 5 1. A crosslinking agent containing a group of formula
 (I)



10

[in which each X, which may be the same or different, is selected from -O-, -S- and -NR-, where R represents a hydrogen atom or an organic group; each Y, which may be the same or different, represents carbonyl, thiocarbonyl, sulphonyl or phosphoryl (i.e. a group of formula

20

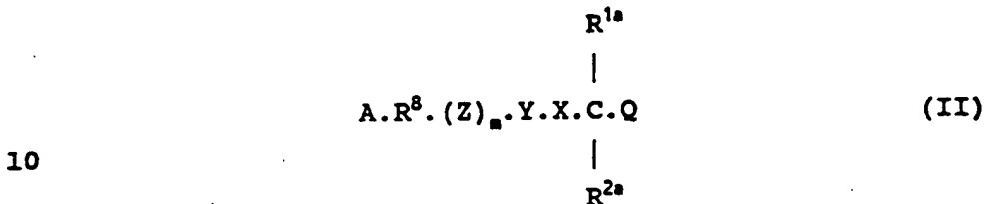


25 where R³ is a hydrogen atom or an organic group) or a similar acid-forming group; each Z, which may be the same or different, is selected from -O-, -S- and -NR-, where R represents a hydrogen atom or an organic group; m and n, which may be the same or different, are each zero or 1; and R¹ and R², which may be the same or different, are each selected from hydrogen atoms, monovalent organic groups and groups of formula -X.Y.(Z)_m- as hereinbefore defined, or R¹ and R² together form a divalent organic group] or containing a group
 30 adapted to generate a group of formula (I) upon reaction with a reagent or substrate containing a species H.X.Y.(Z)_m- or a reactive derivative thereof with the proviso that when the grouping of formula (I) is
 35

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attached to two optionally substituted lower alk-1-enyl groups, both of X represent -O- or -NR- and both of Y represents -CO-, then at least one of m and n is 1.

- 5 2. A crosslinking agent as claimed in claim 1 of the formula (II)



(wherein Q is a leaving group L or a group of formula -X.Y.(Z)_n.R⁹.B; X, Y, Z, m and n are as defined in claim 1; R^{1a} and R^{2a} are as defined for R¹ and R² in claim 1 except that they may represent groups -X.Y.(Z)_m.R⁸.A or -X.Y.(Z)_n.R⁹.B rather than groups -X.Y.(Z)_m-; R⁸ and R⁹, which may be the same or different, represent divalent organic groups optionally interrupted by one or more heteroatoms and/or carrying one or more substituents containing heteroatoms; and A and B, which may be the same or different, optionally in conjunction with the groups R⁸ and R⁹ to which they are attached, represent functional groupings reactive with the species to be crosslinked; with the proviso that when both A.R⁸- and -R⁹.B represent optionally substituted lower alk-1-enyl groups, both of X represent -O- or -NR- and both of Y represent -CO-, then at least one of m and n is 1).

- 30 3. A crosslinking agent as claimed in claim 1 or claim 2 in which each X is -O- and each Y is -CO-.

4. A crosslinking agent as claimed in any of claims 1 to 3 in which R, R¹, R² and R³ are each selected from hydrogen atoms and aliphatic, cycloalkyl, araliphatic, aryl and heterocyclic groups.

5. A crosslinking agent as claimed in any of claims 1

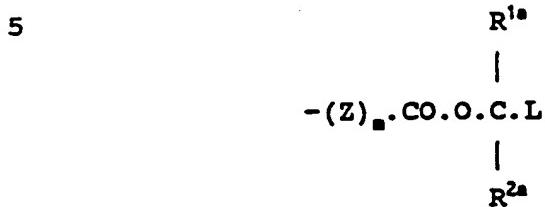
- 43 -

to 3 in which R, R¹, R² and R³ are selected from hydrogen atoms and C₁₋₄ alkyl groups.

6. A crosslinking agent as claimed in any of claims 2
5 to 5 in which R⁸ and R⁹ (where present) are selected from alkylene groups, alkenylene groups, cycloalkylene groups, arylene groups, aralkylene groups and heterocyclic groups, any of which may be substituted and/or be interrupted by heteroatoms.
- 10 7. A crosslinking agent as claimed in any of claims 2 to 6 in which R⁸ and R⁹ (where present) are each selected from C₁₋₃₀ alkylene optionally interrupted by one or more oxy, carbonyloxy or oxycarbonyl groups; phenylene; phenyleneoxy and phenyleneethynyl groups.
- 15 8. A crosslinking agent as claimed in any of claims 2 to 7 in which A or B (where present) are selected from halogen atoms, aryl halides, sulphonyloxy groups, α-
20 halomethyl carbonyl groups, carboxyl groups, activated carboxyl groups, hydroxyl groups, activated hydroxyl groups, mercapto groups, alkene groups, activated alkene groups, conjugated diyne systems, conjugated enyne systems, epoxy groups, acetal-forming aldehyde and
25 ketone groups and derivatives thereof, amino groups, diazo groups, imidoester groups alkyl and aralkyl halide groups, nitroaryl halide groups, nitrene precursor groups, carbene precursor groups, aldehyde groups, ketone groups, isocyanate groups, isothiocyanate groups, semicarbazide groups, thiosemicarbazide groups,
30 phenol ester groups, acyl azide groups, hydrazine groups, haloformate groups, optionally sulphonated maleimide groups, nitrosourea groups, s-triazine groups, aziridine groups and pyridyl disulphide groups.
- 35 9. A crosslinking agent as claimed in claim 8 in which A and B (where present) are O-linked sulphonated N-hydroxysuccinimidyl residues.

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10. A crosslinking agent as claimed in claim 2 in which L is a leaving group and $-R^6A$ terminates in a grouping



10 (where m , Z , R^{1a} , R^{2a} and L have the meanings given in
claim 2).

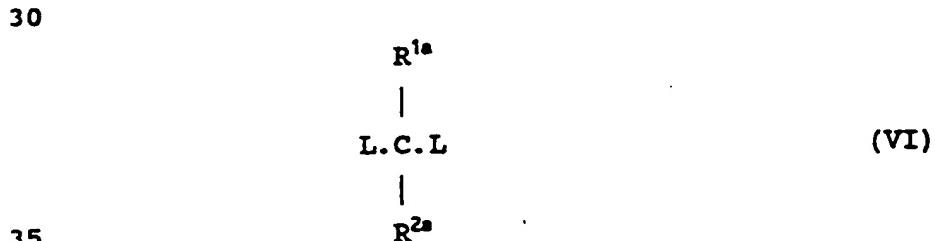
11. A crosslinking agent as claimed in any of claims 2
15 to 10 in which L is a halogen atom.

12. A process for the preparation of a crosslinking agent as defined in claim 2 in which

20 (A) either one or two equivalents of a compound of formula (V)



25 (where X, Y, Z, m, R⁸ and A are as defined in claim 2,
subject if necessary and/or desired to any reactive
groups being protected) or a functional derivative
thereof are caused to react with one equivalent of a
compound of formula (VI)

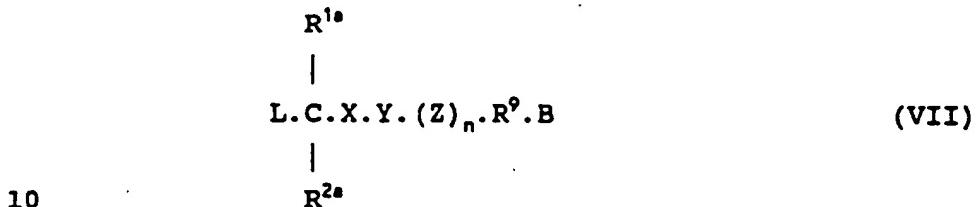


(where R^{1a} , R^{2a} and L are as defined in claim 2 and the substituents L may be the same or different);

- 45 -

(B) one equivalent of a compound of formula (V) as defined in (A) above or a protected and/or functional derivative thereof is caused to react with one equivalent of a compound of formula (VII)

5



10

(where X, Y, Z, n, R^{1a}, R^{2a}, B and L are as defined in (A) above, subject if necessary and/or desired to any reactive groups being protected);

15

(C) for the production of symmetrical compounds of formula (II) in which R^{2a} is hydrogen, m and n are zero, each Y represents a carbonyl group and each X represents -O-, a compound of formula (VIII)

20



25

(where A and R⁸ are as defined in (A) above, subject if necessary and/or desired to A and any other reactive groups being protected) is caused to react with an aldehyde of formula (IX)



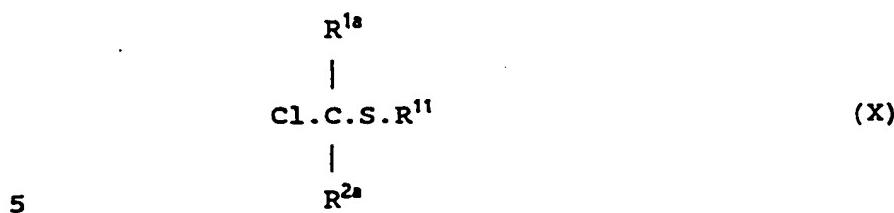
30

(where R^{1a} is as defined in (A) above) in the presence of an acid catalyst;

35

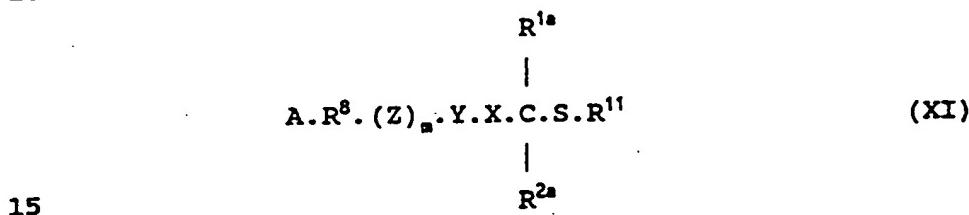
(D) for the production of compounds of formula (II) in which L is a halogen atom, a compound of formula (V) as defined in (A) above or a protected and/or functional derivative thereof is caused to react with an aryl thioether of formula (X)

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(where R^{1a} and R^{2a} are as defined in (A) above and R^{11} represents an aryl group) to form a compound of formula (XI)

10

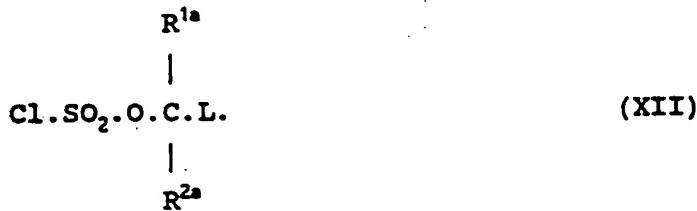


(where X, Y, Z, m, R^{1a} , R^{2a} , R^8 and R^{11} are as hereinbefore defined) and the latter compound (XI) is caused to react with a halogenating agent;

20

(E) for the production of compounds of formula (II) in which Q is a leaving group L, a chlorosulphate of formula (XII)

25



30

(where R^{1a} , R^{2a} and L are as defined in (A) above) is caused to react with a compound of formula (V) as defined in (A) above or a protected and/or functional derivative thereof;

35

(F) for the production of compounds of formula (II) in which L is a halogen atom, a compound of formula (XIII)

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(where R^{1a} , R^{2a} and X have the meanings given in (A) above) is caused to react with a compound of formula (XIV)

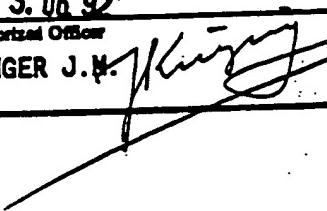
10 Hal.Y. (Z)_n.R⁹.B (XIV)

(where Hal is a halogen atom and Y, Z, n, R⁹ and B have the meanings given in (A) above);

15 followed where necessary and/or desired by removal of
protecting groups and/or interconversion of reactive
groupings A and/or B.

13. Use of a crosslinking agent as claimed in any of
20 claims 1 to 11, including crosslinking agents not
subject to the proviso in claim 1, to prepare substrates
containing biodegradable crosslinkages.

14. Use as claimed in claim 13 wherein the substrate is
25 an ultrasound contrast agent.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07C69/96; A61K49/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Indicated in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 083 185 (MOBIL OIL CORPORATION) 6 July 1983 see claims 1-5 -----	1
<p>* Special categories of cited documents :¹⁴</p> <ul style="list-style-type: none"> "A" document defining the general state of the art which is not considered to be of particular relevance "D" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "T" document published prior to the international filing date but later than the priority date claimed <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Data of the Actual Completion of the International Search 1 04 JUNE 1992	Data of Mailing of this International Search Report 23.06.92	
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer KINZINGER J.M. 	

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9200717
SA 57661

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date		Patent family member(s)	Publication date
EP-A-0083185	06-07-83		AU-A- 9180582 JP-A- 58145729	07-07-83 30-08-83

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4.76 (CH, t), 5.70 (CH₂, s). ¹³C NMR (300 MHz, CDCl₃): δ 38.52 (CH₂), 53.37 (CH₃O), 79.02 (OCH₂O), 168.32 (C=O).

5 EXAMPLE 20

Methylene bis(3-methoxypropenoate)

Methylene bis(3,3-dimethoxypropionate) (14.01g, 50 mmol) prepared as described in Example 19 and a catalytic amount of p-toluene sulfonic acid is added to toluene (250 ml). The methanol is removed by warming the reaction under an N₂ atmosphere. When the reaction is complete the toluene is distilled off under reduced pressure. Diethyl ether (250 ml) is added and the mixture is washed with saturated aqueous sodium hydrogen carbonate (5x50 ml) and water (3x50 ml). The organic layer is dried (MgSO₄) before evaporation to give 8.52g (79%) product. ¹H NMR (300 MHz, CDCl₃): δ 3.65 (2 x CH₃, s), 5.2 (2 x CH, d), 5.8 (O-CH₂-O), 7.65 (2 x CH₂, d).

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EXAMPLE 21

Methylene bis(10-undecenoate)

25 10-Undecylenic acid (12.75 g, 75 mmol) is dissolved in 100 ml water. Cesium carbonate (13.04 g, 40 mmol) is added to the mixture. The water is removed under reduced pressure and the salt dried for 2 hours in vacuo. The cesium salt is mixed with 150 ml DMF and diiodomethane is added to the solution. The reaction is stirred for 3 days at 60°C under an N₂ atmosphere. DMF is then removed under reduced pressure. The residue is purified through silica gel with hexane/ ethyl acetate (8:2) as eluant. The solvent is evaporated to give 7.18 g (54%) product. ¹H NMR (300 MHz, CDCl₃): δ 1.2-1.4 (10 x CH₂, m), 1.6 (2 x CH₂, m), 2.0 (2 x CH₂, m), 2.19 (2 x CH₂, t), 4.9 (2 x H₂C=, m), 5.88 (O-CH₂-O, s), 5.9 (2 x